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Chemistry was the subject of the 63rd Lindau Nobel Laureate Meeting this summer, and there was no doubting the human chemistry on the tiny German island of Lindau. Participants were absorbed by the lectures and engaged in effervescent conversation in the atrium, with interactions catalysed by ancillary events.

Many of the 34 Nobel laureates were making their second, third or umpteenth visit to the annual gathering, eager to be challenged by the young minds in attendance and inspired by the beautiful emerald-green waters of Lake Constance that surround Lindau. This year there was a non-scientific laureate in their number: José Ramos-Horta, joint recipient of the 1996 Nobel Peace Prize. Although peace prizewinners have attended the meeting before, this was the first time for the former Prime Minister of East Timor. This was also the first visit for Brian Kobilka, one of the newest laureates. Kobilka gave the opening lecture on G-protein-coupled receptors (GPCRs), which are the target of around a third of all pharmaceuticals. His work in determining the first GPCR structures should have big implications for future drug development (S50).

For the 625 young researchers at Lindau, this was a rare chance to rub shoulders with the scientific elite: to learn from, debate with and be inspired by their stories. The Nature Video team set up four debates between laureates and students, one of which — on the topic of biofuels — is continued in this Outlook (S60).

Finally, we have Q&As with five of the chemistry Nobel laureates (beginning on S53). This year the interviews were conducted and written by young researchers.

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Michelle Grayson
Senior Editor, Supplements

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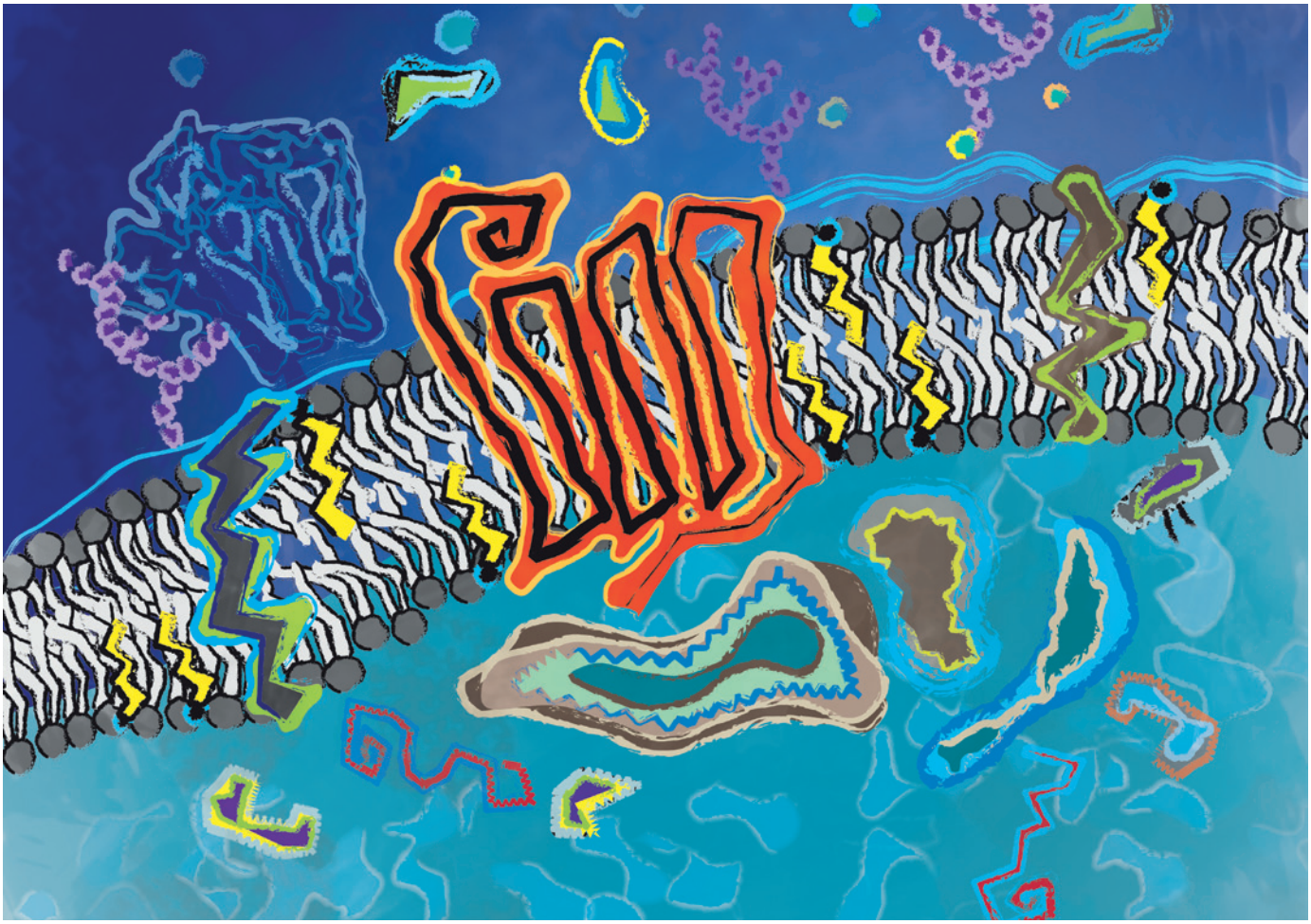

SCRIPPS GPCR NETWORK

An G-protein-coupled receptor with its seven transmembrane domains, by Katya Kadyshevskaya of the Scripps GPCR Network

DRUG DISCOVERY

Structure-led design

Knowing the structures of G-protein-coupled receptors, says Lindau keynote speaker Brian Kobilka, should help with drug development. But how is this progressing?

BY MONICA HOYOS FLIGHT

Brian Kobilka, with his medical background, said he felt like the "the new kid in the chemistry club" at this summer's Lindau Meeting. But it's likely that every attendee was already familiar with his Nobel prizewinning work on the structure of the G-protein-coupled receptor (GPCR) for the hormone adrenaline. This research has "revolutionized the hunt for new GPCR-ergic drugs", and has the potential to improve the treatment of many diseases, says Bryan Roth, a structural biologist and molecular pharmacologist at the University of North Carolina in Chapel Hill.

GPCRs regulate the response of virtually every cell in the body to a wide variety of signals, including hormones, neurotransmitters, ions, odour molecules and even light. When they are activated by the right molecule (or ligand) GPCRs undergo a structural change that triggers a chain of reactions in the cell. By targeting different members of the GPCR family, drugs can have a huge variety of physiological effects. For example, beta blockers can slow the heart rate; antihistamines can prevent allergic reactions; and antipsychotics can modulate neurotransmission. As such, GPCRs present a wealth of opportunities for drug development. Indeed, it is their importance as targets of intensive-care medicines that lured Kobilka out of the clinic and into the lab.

Lefkowitz and Kobilka's work revealed the common structure that underlies the GPCR family as well as the variation among its members (see 'Eureka moment'). Armed with this knowledge, medicinal chemists are starting to design novel ligands that bind to a specific receptor and alter its activity more effectively than existing drugs. This work transcends disciplinary boundaries. According to Arthur Christopoulos, a pharmacologist at Monash University, Melbourne, Australia, translating the biological data into advances in drug discovery will require "biologists and chemists to work closely and speak a common language". Christopoulos is one of many researchers who are aiming to use the emerging information about GPCRs to end the reign of "blunt hammer"

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For some of the latest research on GPCRs, see:
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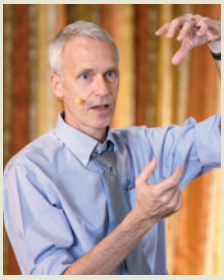
EUREKA MOMENT

The small discovery that hinted at something bigger

In 1968, Robert Lefkowitz tagged hormones with radioactive iodine molecules and showed that the hormones could bind to a receptor outside a cell and trigger a reaction inside it — demonstrating for the first time the existence of biologically active receptors. Brian Kobilka joined Lefkowitz's team in the 1980s with the aim of isolating the gene that encodes the receptor for the hormone adrenaline, which has a key role in the regulation of cardiovascular function. In 1986, they succeeded in cloning the β2-adrenergic receptor and realized that it was very similar to the light-detecting receptor, rhodopsin; both had multiple membrane-spanning domains and large hydrophobic stretches. This similarity suggested that the β-adrenergic receptor was part of a bigger family of receptors that are structurally related but have completely different functions. These soon became known as G-protein-coupled receptors (GPCRs).



CHRISTIAN FLEMMING/LINDAU NOBEL LAUREATE MEETINGS

Brian Kobilka

Since this 'eureka' moment, more than 800 genes encoding GPCRs have been identified, and 23 structures have been solved (see 'Time and Space). Most of these structures are for receptors in the class A (Rhodopsin-like) family, which includes adrenergic, muscarinic and opioid receptors — established targets for drugs that treat cardiac or respiratory arrest and pain. But GPCRs are notoriously difficult to isolate and crystallize. Not only are they highly insoluble but they are also dynamic — their structure is constantly changing as they interact with different ligands and intracellular signalling proteins. It was only in 2011 that Kobilka managed to crystalize the human β2-adrenergic receptor at the exact moment of activation when, bound to a ligand and a G protein, it sends a signal into the cell[4].

Recently, the structures of receptors from different families have been reported. These include the smoothened receptor (SMO), the first in the frizzled class[5]; and two from class B — the corticotropin-releasing factor 1 receptor (CRF1R) and the glucagon receptor[6,7]. These receptors are clinically validated targets for diseases such as cancer and type 2 diabetes but, owing to their large ligand-binding surfaces, conventional approaches have struggled to generate small-molecule drugs against them. ***M.H.-F.***

medicines; they hope to design new drugs targeting GPCRs that will be potent enough to offer better treatment and selective enough to eliminate side-effects.

A PRECISION TOOL

Drug development is slow and expensive. Fewer than 5% of the molecules that enter phase I clinical trials are eventually approved by the US Food and Drug Administration; each drug that makes it is estimated to cost its manufacturer close to US$1 billion. Until recently most drugs, including those that target GPCRs, were formulated with only a limited understanding of the underlying structure and biology of their targets.

The most successful attempts at GPCR drug discovery have targeted receptors that are activated by small molecules such as adrenaline or serotonin, for which high-throughput screening of chemical entities has found analogues. The adrenaline receptor agonist salbutamol, for example, was first approved 45 years ago and remains one of the most effective agents for asthma. However, it is more challenging to develop small molecules with drug-like properties that fit the binding sites of GPCRs with larger protein or peptide ligands. And, given the underlying similarity among GPCRs, it is nearly impossible to identify selective drugs that don't have any unanticipated off-target actions.

Researchers hope that working backwards from a receptor's structure will advance the development of new drugs. Several companies are using structural information about receptors' binding pockets to feed into virtual screening programs, sometimes building drugs up from smaller fragments. By identifying regions of the binding pocket that are unique to each receptor, researchers can design highly selective ligands — the first step in the development of drugs for targets that were previously considered undruggable. "These approaches can lead to highly optimized drug candidates with improved efficiency," says Fiona Marshall, chief scientific officer of drug discovery company Heptares Therapeutics, based in Welwyn Garden City, UK.

GPCRs, says Marshall, are also emerging as targets for rare diseases that currently lack any drugs at all. So-called 'orphan receptors' (GPCRs for which the natural ligand is not known) are also attractive drug targets. Heptares is working on the structure of recently 'de-orphanized' receptors and has identified agonists for GPR39, which is involved in islet cell function and is a target for diabetes therapies. "This receptor is particularly interesting in that it has the potential to halt the progression of the disease," she explains. In addition, Heptares is using stabilized pure GPCR preparations to generate antibodies that either activate or silence receptors with large binding pockets, in collaboration with companies such as MorphoSys and MedImmune. These therapeutic antibodies offer many advantages as drugs. "Antibodies can have unique specificity and a long-lasting action, and they can be coupled to other modalities such as drug conjugates for cancer," says Marshall. A number of such antibodies developed by other companies are in clinical trials[1] and mogamulizumab, a drug marketed as Poteligeo by Tokyo-based biotech company Kyowa Hakko Kirin, has already been approved in Japan for the treatment of adult T-cell leukaemia.

> ***"These approaches can lead to highly optimized drug candidates with improved efficiency."***

CHANGING LANDSCAPE

Structural research has revealed other layers of complexity for GPCRs. In addition to the binding site for the endogenous ligand (orthosteric site), GPCRs have allosteric sites, where other molecules can bind. Allosteric sites are more structurally diverse than orthosteric sites, and provide opportunities to fine-tune the activity of GPCRs. However, it is hard to quantify allosteric effects, especially when, for many GPCR targets, the level of signalling needed for optimal therapeutic benefit is unknown. This is an exciting area: "If we can understand how receptor signalling links to clinical outcomes, we will have a better handle on the desired signalling properties of drugs," explains Patrick Sexton, a pharmacologist at Monash University in Melbourne, Australia.

Two allosteric ligands are currently approved as therapeutic agents: cinacalcet (marketed as Sensipar by Amgen, based in Thousand Oaks, California), which activates calcium-sensing receptors and is used to treat hyperparathyroidism; and maraviroc (marketed as Celsentri/Selzentry by UK-based ViiV Healthcare), which blocks the chemokine receptor used by HIV to gain entry into host cells. A number of small companies are investigating allosteric modulators of GPCRs for the treatment of neurodegenerative and

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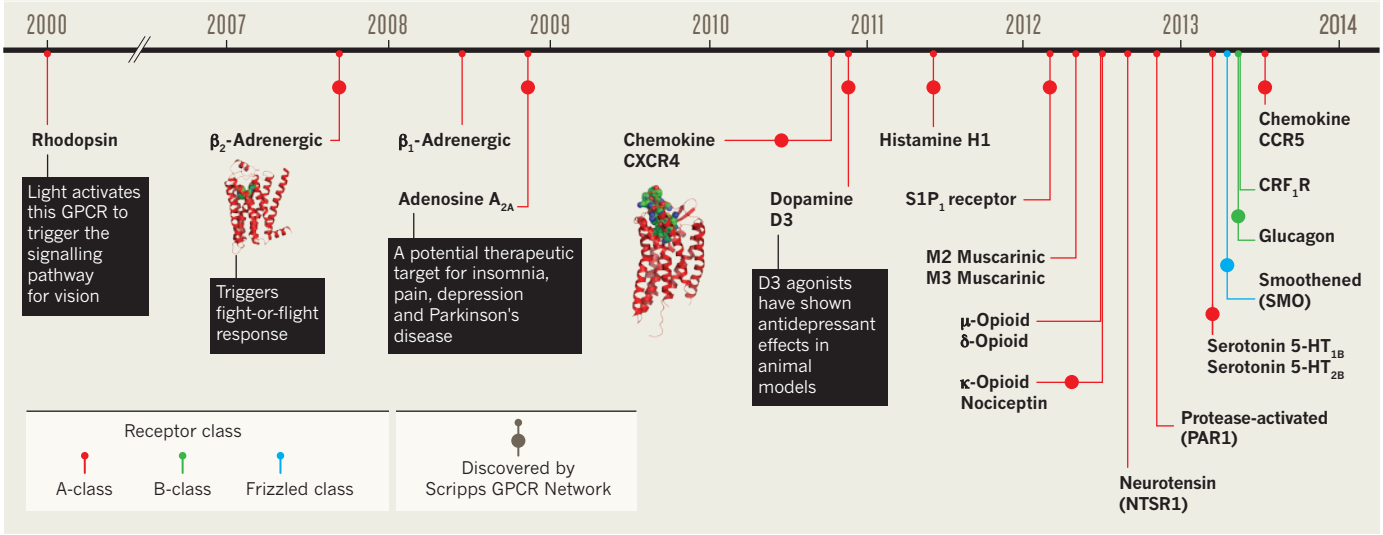
TIME AND SPACE

The number of solved structures is rapidly increasing, mainly owing to the efforts of the Scripps GPCR Network. Established in 2008, the network is a large-scale collaboration involving more than a dozen academic and industrial labs. Its goal is to characterize at least 15 GPCRs by 2015; it has already solved 13.



STRUCTURES: SCRIPPS GPCR NETWORK

psychiatric diseases. Addex Therapeutics, based in Geneva, has two such compounds in phase II trials, targeted at different metabotropic glutamate receptors (excitatory receptors on neurons, also called mGluRs). Dipraglurant is an inhibitor of mGluR5 that can reverse levodopa-induced dyskinesia in patients with Parkinson's disease and is being evaluated as a treatment for rare dystonias; and ADX71149, which activates mGluR2, can reduce anxiety and the negative symptoms of schizophrenia and is being developed with partner Janssen Pharmaceuticals. "These compounds show great receptor subtype selectivity compared to orthosteric ligands," says Tim Dyer, Chief Executive Officer of Addex.

Further drug selectivity might be achieved with compounds that act simultaneously on both orthosteric and allosteric binding sites. Although such bitopic ligands have been identified in the lab, none has entered clinical trials. Christopoulous has suggested that this strategy might work against the M1 muscarinic acetylcholine receptor, a promising target for the treatment of cognitive deficits that has so far proved undruggable[2]. However, research on bitopic ligands is still in the early stages. Among the most important challenges, says Christopoulous, is figuring out how best to link the two ligands for the orthosteric and allosteric sites. Such conjoined molecules might be "too large to be appropriately optimized and developed as potential drug leads", he adds.

SIGNAL SNAPSHOTS

Structural studies have shown that GPCRs can adopt different conformations depending on which ligand they are bound to. What's more, the structure adopted by the receptor influences the signalling pathway that is activated in the cell. The main pathways go through guanosine nucleotide-binding proteins (G proteins) to trigger metabolic processes. But GPCRs can also bind to arrestin and prevent the activation of G proteins, causing the receptor to retreat inside the cell or to activate alternative signalling pathways. Ligands that trigger just one of these pathways are said to induce biased signalling.

Sexton is investigating whether biased signalling can lead to better drugs. For example, he suspects that the reason why the beta-blocker carvedilol is more effective than other drugs in the same class is because it can induce signalling through arrestins. How this leads to a greater therapeutic benefit is unclear but, "as we understand more about the link between signalling and physiology we can expect increasing numbers of programmes to develop biased ligands", he says. To this end, his lab is examining the effects of such ligands in different tissues and in transgenic animals with receptors that have been modified to respond to natural ligands with biased signalling.

"The next five years will see an increase in the number of receptors crystallized."

Roth's lab is focusing on the design of GPCR drugs that activate arrestin. "Already we have evidence that such drugs have the potential to revolutionize treatment for a number of common diseases including schizophrenia, cardiovascular disease and chronic pain," he says. Roth is working with Jian Jin, a medicinal chemist at the University of North Carolina who is in the interdisciplinary center for Integrative Chemical Biology and Drug Discovery. Roth and Jin recently described the first β-arrestin-biased dopamine D2 receptor agonists, which have robust antipsychotic drug-like activity in preclinical models[3]. "We are in the process of evaluating potential clinical candidates," Roth says. "Things are progressing nicely."

Nicely — but slowly: drug discovery and development based on GPCR structures "are at an early stage", says Marshall. There are numerous targets and they are difficult to crystallize. What's more, these GPCR structures are static snapshots of receptors that are in constant flux. "The dynamic nature of GPCRs should be factored into computational approaches towards drug design," notes Christopoulos. "Otherwise we will run into the same problems with low success rates that others have had in the past."

Still, Sexton is optimistic and predicts that the next five years will see an increase in both the number of receptors crystallized and the quantitative tools used to describe effects such as signal bias and allostery. These, he adds, "will progressively have an impact on drug candidate selection". As the crossover between biology and chemistry continues, it is unlikely that Kobilka will remain the new kid in the chemistry club for long. ■

Monica Hoyos Flight *is a writer and editor on* Nature Reviews Neuroscience *and* Nature Reviews Drug Discovery *in London.*

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M GRAYSON

Q&A Gerhard Ertl

A lateral thinker

The winner of the 2007 Nobel Prize in Chemistry ponders biology's big questions with Diane Wu.

When you were a student, did you meet any of your scientific heroes?
I met physicist Frédéric Joliot-Curie. I was studying at the University of Stuttgart and in my second year a friend suggested that we go and study in Paris. This was quite an adventure. We attended lectures by Joliot, who was a very spirited and energetic man (although he was already sick, and died one year later). I never forgot his lectures: "Today we ask the question, what is nothing? Quel est rien?" Nobody knew how to answer. But that was how he introduced the neutron to us — the neutron is a "nothing" of charge.

M GRAYSON

"The big fundamental problems today are in physics and biology."

In 1959, I spent a year at the University of Munich where Werner Heisenberg taught quantum mechanics. There were at least 300 students in the class, and it was hard to follow. We had to solve problems and, if you were successful, you got a certificate: "You participated in the exercise of quantum mechanics", signed by Heisenberg. I value mine very highly and still have it today.

What are the big questions in chemistry today?
Chemistry doesn't have any really big fundamental problems. The last big question in chemistry was 'what is the nature of the chemical bond?' — and that was answered almost 100 years ago with the advent of quantum mechanics. The big fundamental problems today are in physics and biology.

In physics, the big question is: how can the two great theories in physics — quantum physics and the theory of gravitation — be unified? There are other questions: what is the content of our Universe? What are dark matter and dark energy? Only four per cent of the Universe is the matter that we are made of; what is the rest?

In biology, there is: what is life? We know which elements are important for life, but will it ever be possible for humans to create artificial life? These are the big questions. Chemistry has nothing compared with this.

Erwin Schrodinger posed the question 'what is life?' seventy years ago in his book of the same title. How close have we come to answering it?
The question that Schrodinger was asking was very specific — in essence, do we expect that new laws will be necessary to describe biology? And he couldn't give an answer, mainly because he was not able to explain the formation of structure in biology. Not only molecular structure, but larger structures as well – for example, how does a cell divide only in the middle? We can start to answer these questions using non-linear dynamics — and that is the field that interests me the most.

What is the importance of structure to life?
Self-organization is the basis for all kinds of structure formation. Closed systems that have no external inputs will eventually find a state of equilibrium that can be disordered or ordered. For example, salt ions precipitating out of a solution can assemble into ordered crystals. Open systems have a continuous inflow of energy, which allows them to hold a position away from equilibrium. For example, a cell has an inflow of energy in the form of food, which allows it to maintain its structure and function. The mathematical description of these processes requires non-linear differential equations, ▶

Gerhard Ertl won the Nobel Prize in Chemistry in 2007 for elucidating what happens at the molecular level at solid–gas interfaces. His pioneering work established the field of surface science. Ertl is now professor emeritus at the Department of Physical Chemistry, Fritz-Haber-Institut der Max-Planck-Gesellschaft in Berlin.

Diane Wu is a graduate student at Stanford University. She researches upconverting materials, which convert light from lower to higher energies and have nascent applications in bioimaging and solar energy conversion.

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AIP

Patterns of gas on a platinum surface

so it is often called non-linear dynamics. Studying biological systems using non-linear dynamics shows that existing physical laws are sufficient to describe order in living systems — just as Schrodinger predicted but could not prove.

How did you come to be interested in non-linear dynamics?

Twenty-five years ago, I was working on reactions at surfaces, and came across a well-known problem: reactions on a surface often show illogical behaviour. For example, in an open system with constant inflow, you would expect constant outflow. But sometimes the outflow becomes oscillatory. That's a consequence of the complexity of the chemical reaction, and is based on the underlying non-linearity of the equations used to describe the kinetics.

What mysteries in biology besides structure formation can be addressed with non-linear dynamics?

Theoretical physicists are helping to answer many medical questions. For example, the electric pulses of the heart are chaotic and can be analysed and modelled with the tools of complexity.

Cardiac pulses are not localized — they are electric currents that spread across the whole heart in waves. These waves propagate through a chemical reaction coupled to electric phenomena. One of the pioneers of describing this field of complexity was cardiologist Arturo Rosenblueth who, together with mathematician Norbert Wiener, wrote a paper about how this kind of pattern might emerge. Researchers in medicine are interested in in dynamic systems in the body, and how they respond in a non-linear way to various inputs. Complexity can be used to describe and predict this kind of physiological response.

I'm working on a book which summarizes our knowledge about complexity in different fields. I hope to arrive at one unifying concept that can be applied to different phenomena. ■

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M GRAYSON

Q&A Dan Shechtman

The technology starter

The winner of the 2011 Nobel Prize in Chemistry speaks to Valerie Gerard about creating leaders and achieving prosperity though technological entrepreneurship.

What does it mean to you to have won the Nobel prize?

I see everything that happens in my life as an opportunity. With the Nobel prize comes the opportunity to talk to people around the world. I am on a mission to talk to other scientists, to students, to decision makers, and to the population in general about the importance of education for all, and in particular good science and engineering education and of technological entrepreneurship. Many people around the world are disenchanted because they do not see a future. We need leaders, at all levels of society, to show these people the way forward.

How can we find these leaders?

We have to make them. The first thing to do is to teach them to be good human beings. Young people today are surrounded by mirrors; wherever they look, they see themselves. We need to break the mirror and let them see what other people need, understand where they come from, and communicate. Then we have to build a leadership character, to let young people take on responsibilities at junior levels and then rise to

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the top. If these young people become the real decision makers, we will have a better world.

What can we do for those countries that are not succeeding?

Education for all is job one. To provide good standards of living, we need scientists and engineers. Don't get me wrong, we also need musicians, poets, writers and film makers to give taste to life. To live in good economic conditions, however, we need technology people who are motivated to start companies.

It is in the interest of developed countries to make sure education reaches all rural and disadvantaged parts of the world. In Europe, the average number of children is around 1.5 per woman, and in some Far East countries it is closer to one child. But in central Africa, the average number of children per woman is very high — in Niger, for example, it is 7. This imbalance results in waves of immigrants and refugees. The main factors that limit the number of children are education for women and urbanization.

What is the role of technological entrepreneurship in improving a country's economy?

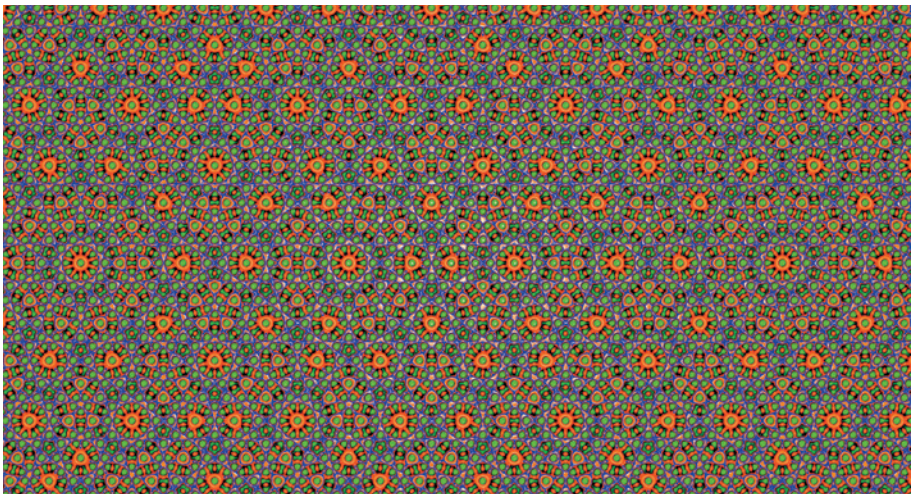
When start-ups grow, they can double their workforce each year. They are a great way to boost employment of educated people. Those with less education might appear to have more limited chances, but they can also become entrepreneurs: for example, they can open shops or provide services. Entrepreneurship should be promoted by governments everywhere, through education and support. I am against too much government intervention in business, but they should support entrepreneurship.

"The value of your company now is exactly zero. Be generous with that zero."

How are entrepreneurs made?

I have been teaching technological entrepreneurship for 27 years at the Technion in Israel. It is a large class open to all students. I show the students the stepping stones to success, where the stumbling blocks are and how to jump over them. I developed this class even though it is not my profession — I am a materials scientist — because entrepreneurship is important for my country. In that period Israel has become a start-up nation: according to Saul Singer, co-author of the book *Start Up Nation: The Story of Israel's Economic Miracle* (Twelve, 2009), "Israel has more start-ups per capita than anywhere else outside Silicon Valley."

I like to think that I have something to do with it. In entrepreneurship, there is the know-how, which can be taught, and there is the spirit of entrepreneurship, which comes with knowledge and can be greatly promoted by role models. In Israel we know about entrepreneurship and many feel that it is a good idea to become an entrepreneur. It's our national sport.



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Computer model of a quasicrystal pattern, which shows order but is not periodic.

What are the risks associated with starting up a business?

Most start-ups fail. We tell the students that failure is OK. We obviously don't recommend failure, but if you fail, it is not personal, it is not a shame. If you fail, you start again. You failed either because you made a mistake, which you will not make again, or because of something that you could not foresee, like a shift in the market. I trust you more than a novice to entrepreneurship because you have been through the process; you are now an experienced entrepreneur.

How can someone avoid the common pitfalls of financing a start-up?

We teach our students where to get money and what money not to touch. Not all money is the same. For instance, never touch your own money, and never take money from your relatives or friends because there is a good chance that you will lose your relatives and your friends. Good money comes with good advice or with help in marketing, from strategic partners or business angels who trust your idea and want to work with you. I have a problem with venture capitalists: although they can make a lot of money available, they want their money back too soon — within five years. In five years you cannot strive, you cannot build your start-up to become a good, large company.

Or you can do boot-strapping: working without money. You might need other people's expertise and without money you cannot pay for it. But you do have something valuable that you can share: your company. Give them a share of your company, and be generous. The value of your company now is exactly zero. Be generous with that zero. If you are successful, in the end there will be plenty of money for everybody.

Could anyone become an entrepreneur?

It depends on character. I am an entrepreneur by nature. As a hobby I make jewellery; when I make a new piece, I immediately think of the process that will make 10,000 pieces. Not everybody should become an entrepreneur, but entrepreneurship should be promoted all around the world, for our well-being.

Is industrial research a good option for those non-entrepreneur scientists?

Industries today lead a lot of excellent research because they have their feet on the ground; they know what is needed for their next product to sell. Universities have the advantage of studying esoteric subjects that industry would not consider, which sometimes bring interesting results. I have never worked for industry but I think that, today, working for a good company is a fantastic opportunity for a researcher. After all, the number of professorships around the world is limited. ■

Dan Shechtman won a Nobel prize for the discovery of quasi-periodic crystals (structures that are ordered but not periodic), which revolutionized the field of crystallography. He is now the Philip Tobias Distinguished Professor of Materials Science at the Technion–Israel Institute of Technology in Haifa, Israel, where he also teaches technological entrepreneurship — a passion of his. He is also a Distinguished Professor at Iowa State University.

Valerie Gerard, a post-doctoral researcher at Trinity College Dublin, Ireland, is developing semiconductor and metal nanoparticle-based composites for biomedical applications.

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NATURE VIDEO

Q&A Robert Grubbs
The bond shifter

Rebecca Melen talks to the joint winner of the 2005 Nobel Prize in Chemistry about how his research is being applied to many different processes.

What was your introduction to organometallic chemistry?

Early in my undergraduate organic chemistry course, at the University of Florida, I heard a talk by a professor from the University of Texas about cyclobutadiene. On its own, cyclobutadiene is extremely reactive and can't be isolated, but you can isolate the metal complex. It struck me as very interesting that metals could stabilize such reactive species.

Later, I moved to Columbia University in New York and trained as a physical organic chemist. But there were many great physical organic chemists doing remarkable things. I recalled that lecture from the Texas professor and found that the organometallic field was still very small: you could read four or five papers and call yourself an organometallic chemist, and stabilizing reactive organic species such as cyclobutadiene was still really exciting. So during my post-doc I decided to switch to organometallics.

In fact, there are a group of us, all about the same age, who trained as physical organic chemists and ended up in organometallic chemistry. We're good friends — and sometimes competitors.

With so many metals to choose from, why did you select ruthenium for your catalyst?

Millions of tonnes of polymers such as Teflon, polythene and polystyrene are produced each year, and catalysts that improve polymer synthesis are crucial. I started my independent research looking at alkene polymerization; in particular, the polymerization of norbornene into poly-norbornene, which is often used as a test substrate for catalysis.

Several reactions produce poly-norbornene from a solution of norbornene and metal salts. The metal salt ruthenium chloride was thought to be a lousy catalyst because it produced polymer so slowly, but one of my students was attracted to it because, unusually, the reaction worked in the presence of ethanol. The hydroxyl group in ethanol (and also in water) is one of the most difficult functional groups for catalysts to deal with, and the reason why adding water often kills catalyst activity.

It was exciting that ruthenium could potentially tolerate the presence of water. Organometallics typically work best without water, so we dried everything out and tried it again but then it didn't work at all! Clearly water was important, and it turned out that using pure water as the solvent was best.

Next, we identified the pre-catalyst (the compound we put into the reaction) and the active catalyst (formed from the pre-catalyst). The active catalyst turned out to be ruthenium carbene complex. Knowing this, we changed the other groups bound to the ruthenium and created catalysts that worked faster and could polymerize other things too. Since then it's just been tinkering and having fun.

Do you see a future for non-precious metals in metathesis?

We've been working on other metal carbenes, including metals with similar electronic properties such as iron, which is cheap, and osmium, which is expensive. You can also use titanium. Richard Schrock has been investigating molybdenum and tungsten. Many of these metal carbenes undergo metathesis. However, the metal is really just a small part of the overall cost. A lot of the expense is in making the ligands and the organometallic catalysts themselves.

Robert Grubbs, a chemist at the California Institute of Technology in Pasadena, was awarded the 2005 Nobel Prize in Chemistry, along with Yves Chauvin and Richard Schrock (see page S59), for the development of olefin metathesis and associated catalysts (primarily ruthenium). Olefin metathesis involves rearranging carbon–carbon double bonds and has widespread applications in fields such as drug synthesis and petroleum reforming.

Rebecca L. Melen completed her PhD in chemistry at the University of Cambridge, UK, and subsequently moved to Toronto, Canada as a postdoctoral fellow. She was recently awarded a Humboldt Fellowship to study at the University of Heidelberg, Germany. Her research focuses on the development of main group metal catalysts for chemical transformations important to both industry and academia.

REBECCA MELEN

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SAMUEL BUCHMANN

Even if we found an iron catalyst for metathesis, I am not sure it would be any better because it would probably have other drawbacks — for example, it would be less stable or active than ruthenium.

What applications and developments do you foresee for olefin metathesis?

I'm particularly happy about a drug that is currently in phase III testing called vaniprevir (from Merck), which is targeted against the hepatitis C virus. Our olefin metathesis catalyst is really important for the formation of this drug. Another application that I am excited about, and that I spoke about at the Lindau meeting, is the use of metathesis in pheromone synthesis. This might allow toxic and unselective pesticides to be replaced by naturally occurring pheromones that can, for example, disrupt mating patterns in selected insects. My intuition tells me that this is going to be big — but most of it is out of my hands.

Olefin metathesis is an important part of undergraduate chemistry. Do you enjoy lecturing on a topic in which your contribution has been so important?

It's fun to talk about because you can provide a lot of background. I'm not sure the students appreciate it, but that's okay. They don't seem overwhelmed at being taught by a Nobel laureate. At Caltech we have five Nobel laureates on campus — three in chemistry — so it's not a big deal for them.

Is academic science research becoming dependent on industry funding?

Yes, but industry is having similar financial problems to academia and has also cut back on its funding of basic research. Big companies used to help the transition from research in the laboratory to commercialization. When I started doing the early metathesis work, people from big companies would show up and want to test the catalysts. Now, most of the commercialization is done by small companies who are bridging the gap between the laboratory and industry.

What advice do you have for young researchers who wish to pursue a career in academia?

It is a great career if you can get in, but it is tough right now because of funding cuts. It will require particularly dedicated young researchers. Ten years ago, when a researcher entered academia there were good start-up packages, with lots of graduate students and funding. We will probably have to reduce some of that support and make tenure decisions earlier. The day of the really big research group is over. I must admit that I am sort of glad I'm old! ■

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For more on catalysis from Grubbs and Ertl, visit our video archive:
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Q&A Richard R. Ernst

A man of many dimensions

A pioneer of one- and two-dimensional nuclear magnetic resonance (NMR), Ernst talks to Stephanie Harris about why dimensions are important in life as well as in science.

How would you explain NMR to someone without a scientific background?

First, NMR allows you to determine the structure and connectivity of molecules or even to image the human body. NMR works by probing the responses of atomic nuclei in a magnetic field. These nuclei act like spies who give you coded messages that you record with electronic equipment. Once you've recorded these messages, you can try to analyse and understand them.

The nuclei have a magnetic moment, which means they react to an applied magnetic field. When you apply an external magnetic field the nuclei start to precess, or change the orientation of their rotational axis, with a frequency that is proportional to the field strength. If you measure the precessional frequency you can determine the local magnetic field, which differs from the applied magnetic field because of shielding from the electrons that surround the nuclei. The difference between the two fields provides important information about the chemical environment around the nuclei within the molecule — whether it is electron-rich or -poor.

NMR can also tell us about the structure of a molecule: how the nuclei are spatially arranged. This is because the magnetic moments of nearby nuclei perturb the local magnetic field of the nucleus under study, introducing fine structure or splitting of the observed resonance. The precise nature of this splitting — whether it is split into two, three, four or a more complex pattern — tells us how many nuclei surround the one of interest. And the spacing of the lines in the pattern allows us to determine the distance between the nuclei.

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You can obtain a complete picture of the structure of a molecule.

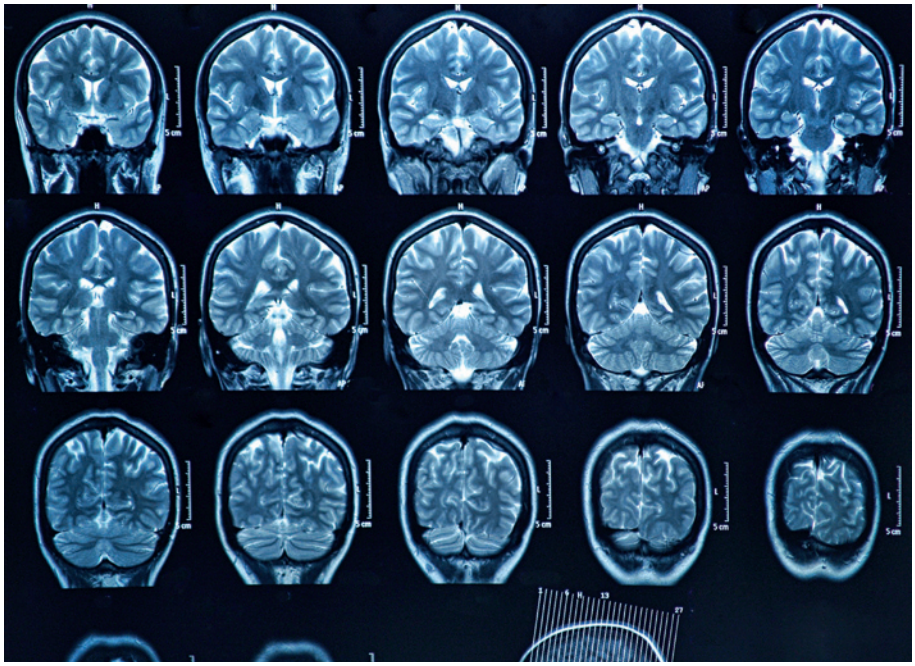
What is the most beautiful use of NMR?
That prize goes to magnetic resonance imaging (MRI), which allows you to peek inside the human body. In fact, MRI has turned out to be important for me personally. Back in 2007, while sitting at my desk, I started to become disoriented. My wife convinced me to go to hospital for a check-up. The doctors used MRI to image my brain and found a stenosis, where the blood vessels narrow and restrict the blood flow. And again, a few years earlier, I was walking down the street when a pain developed in my left leg and foot, and soon I wasn't able to walk any further. My foot turned white. The hospital used MRI to diagnose a blocked artery. By-pass surgery restored it fully.

After finishing your PhD you took a job in industry rather than staying in academia. Was this your plan?
I was fed up with the university atmosphere and wanted a change. I also wanted to leave Switzerland. California was the right place to look for another job. It had to be in industry; I wanted to become a useful member of society and not just an academic playboy. I took a job with Varian Associates in Palo Alto, California, continuing working on NMR development.

After five years I returned to ETH Zurich, where I had studied for my doctorate. That was a mistake: I'd always sworn that I would never go back. After about two years, I had a nervous breakdown. I thought that was the end of my scientific career. I considered going to work in a post office and stamping envelopes. Very slowly after a long struggle with myself, I became a scientist again. But it was hard to start over.

Richard Ernst is a physical chemist and emeritus professor at ETH Zurich, Switzerland. He won the Nobel Prize in Chemistry in 1991 for his work on the development of nuclear magnetic resonance (NMR) as a high-resolution analytical technique. NMR spectroscopy uses the behaviour of nuclei in a magnetic field to determine the chemical environment in which they reside.

Stephanie Harris is a graduate student at the University of Bristol, UK, whose research focuses on ultra fast transient absorption spectroscopy. This technique captures chemical bond breaking and bond making in real time, providing detailed mechanistic information about the progress of a chemical reaction.



ISTOCK

Magnetic resonance imaging, based on Ernst's research, allows us to see inside the human body.

What helped you to regain your interest in science?
I kept my intrinsic curiosity, asking questions and trying to understand what was going on around me. You never understand enough or have solved all the problems so you try to improve your knowledge, and that is what I did. Also, teaching helped; students tell you what they expect from you and you have to try to become a good role model. You need more knowledge to do that. It's the same if you go to a kindergarten and give a lecture: they ask you difficult basic questions that you can't answer. You then know that you are lacking knowledge and this helps you to find your way and grow in the proper direction.

"Good teachers allow you to develop your own personality and ways of learning."

How important is it to maintain a passion outside of science?
Inspiration normally comes from an external source, from somewhere unexpected. Without this kind of inspiration you can become very narrow-minded. If you have a passion outside of science you should be proud of it — it makes life more enjoyable. Too many scientists lose their humanity, in the sense that they only have one focus: their research. Science is not the only aspect to life, there are other exciting aspects too and you have to give them a chance.

How do you try to achieve such balance in your own life?
In the early part of my life it was music that kept me alive. Initially I was playing and composing music, nowadays I'm just listening. It is important to get out of the science lab and do something more for my mind and enjoyment. Recently I have become fascinated by Tibetan painting and have started to collect, study and conserve precious art works.

What makes an effective teacher?
Good teachers allow you to develop your own personality and ways of learning — they set you off on a subject and then say, "Go look for yourself." Bad teachers, on the other hand, think that you should strictly follow what they say, and obey their rules. I have had both sorts of teachers. It's more inspiring and more motivating when you have freedom and are responsible for what you are doing, rather than just obeying orders.

What is an example of a good teaching practice?
The most important thing is that you throw the students into cold water and let them swim for themselves. Don't first teach them the motions on dry land — just throw them in and see what happens. We all learn by doing.

Social responsibility in science is also important to you. Did you take any practical measures to act more responsibly in your research?
In 2005, we held a special public teaching event to mark the 150th anniversary of the ETH Zurich university. We sent 150 professors onto the streets to talk to the public. We constructed tents in the city centre of Zurich and gave around 300 open lectures in 3 weeks. This event taught the public about science but had the added advantage of motivating the professors to think about the public, the public's response to them, and the importance of being exposed to the public. Initially they were sceptical, but by the end they liked it, and they wanted to do it again. ■

M GRAYSON

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Q&A Richard Schrock

A sustainable chemist

Jonathan Moerdyk asks one of the recipients of the 2005 chemistry prize whether olefin metathesis, the field he helped to pioneer, has peaked.

What impresses you most about olefin metathesis?

That it is still developing. It was discovered more than 55 years ago but it took 30 years to make the first well-defined catalyst. The field is growing exponentially. I like its simplicity and 'cleanliness': the only products of olefin metathesis are olefins, and you can reuse or store the olefins generated. You start and end with olefins, so it is a closed loop. Olefins are the backbone of the chemical industry and are common in nature.

Because I am not an organic chemist, I didn't realize for many years how impressive a reaction metathesis is. Now I know how important it is to turn olefins into other olefins — it avoids all the intermediate entities and therefore reduces chemical waste.

M GRAYSON

What are the remaining challenges for olefin metathesis?

Applying olefin metathesis and taking it to its extremes: high temperature, tandem catalysis, fancy molecules, polymer chemistry. Also, selective preparation of molecules — it is always good to know the precise structure of the molecules you're dealing with. For example, it is important to be able to make polymers with one uniform structure; olefin metathesis has achieved this, but only with well-defined catalysts. Distributions are fine, but think of DNA: that's a very well defined species and it does fantastic stuff that it couldn't do if its structure were random.

Why are computer models and theoretical calculations not sufficient for optimizing catalytic processes?

You have to remember that you can get complete selectivity for one product over another based on about a 2-kilocalorie (kcal) difference in energy between two reaction pathways. If you look at all the interactions going on — solvent interactions, interactions within the catalyst and substrates, all of them modulated by temperature and other factors — then 2 kcal is nothing. Even today, no theoretician could confidently predict a reaction to within this limit. And they will have to do a lot better than that — to the sub-kcal level — if they are to really understand everything that goes on in a catalytic reaction: for example, to predict whether a catalyst with one methyl group more or less, or with a slightly different bond angle, will be better than another. I wish the theoreticians luck and hope they can do it, but it's going to be tough.

Are the supplies of catalytic metals for olefin metathesis sufficient?

Abundance and sustainability are crucial for the future of olefin metathesis, as they are for other areas of chemistry. The four metals that we know catalyse metathesis are molybdenum, tungsten, rhenium and ruthenium. Molybdenum and tungsten are plentiful enough not to worry.

Molybdenum production was 250,000 tonnes in 2011 and tungsten was 72,000 tonnes; both are used heavily by industry to make tougher steel. They are not as abundant as iron, but iron catalysts are probably not on the cards in the near future. Rhenium and ruthenium are scarcer — in 2011 production was 49 tonnes and around 20 tonnes, respectively.

What are the concerns associated with using low-abundance metals?

If a new application is developed that involves a rare metal, the price of the metal soars. This happened with rhenium and ruthenium in 2006, when new aerospace and electronics applications for these metals were introduced: the price went up by almost a factor of ten. Now the prices have come back down, but no one wants to be subject to that kind of variation. Pharmaceutical companies in particular are very wary because they are tied to a catalyst. If they can't continue to make a drug with that catalyst, they have to start over; that's impractical when they've already spent ten years and $800 million to develop a compound. There's also the matter of scale. If you want to produce anything on a truly large scale, you need tonnes of catalyst. If a lot of companies want tonnes of a catalyst, there just isn't going to be enough to go around. ■

Richard Schrock is a professor of chemistry at the Massachusetts Institute of Technology in Cambridge. With Robert Grubbs (see page S56) and Yves Chauvin, he was awarded the 2005 Nobel Prize in Chemistry for the development of olefin metathesis — the process of changing carbon–carbon double bonds in olefins. This process has found many applications from the preparation of insect pheromones to the manufacture of high-performance plastics.

Jonathan Moerdyk is beginning his fifth year of graduate school at the University of Texas at Austin, where he is studying the development of carbon-based mimics and alternatives to transition metals for small-molecule activation, synthesis and catalysis.

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M GRAYSON

Hen Dotan, Hatmut Michel, Steven Chu, Stafford Sheehan and Heather Mayes debate the pros and cons of biofuels and solar electricity for Nature Video.

ENERGY

Fuelling the future

Are biofuels the way forward, or should we be looking to advanced solar technologies to power the future? The debate began on Lindau and continues here.

Making liquid biofuel from plant materials is a controversial approach to securing our energy future. At the Lindau Meeting of Nobel Laureates, two laureates and three young researchers debated the science behind biofuels for Nature Video, and they carry on the debate in these pages.

Heather Mayes: The primary message from the biofuels debate is Steven Chu's optimism that our future will be powered by renewable energy, and that biofuels will make a valuable contribution to that future.

In discussing renewable energy options, it is essential to consider the whole process: the resources required, the amount of useful energy created, and requirements for scientific advances or new infrastructure. If we focus too narrowly on one aspect of a technology, we will miss its full promise (and peril). In discussing biofuels, Hartmut Michel concentrated on the fact that plants capture only a small percentage of sunlight, but we do not need to absorb all of the solar energy that reaches the earth — that would vastly exceed humanity's energy needs. It is more important to avoid interfering with the food supply — a problem with maize-derived ethanol that might be overcome by producing biofuels from agricultural and forest wastes instead.

Another issue is the expense and difficulty of transporting bulky biomass and converting it to fuel. The costs of converting biomass waste to fuel have decreased by more than two-thirds since 2001 (refs 1, 2), and transport difficulties can be reduced by building biorefineries near agricultural centres. If these issues can be overcome, biofuels will fill a demand not met by other sources of renewable energy: a liquid fuel that can be distributed through our current infrastructure. Biofuels are also the only alternative to fossil fuels that can provide sufficient energy density for industries such as air travel. With non-food biofuels on the cusp of becoming more affordable and available, we should not turn our back on this promising technology.

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Stafford Sheehan: As Chu pointed out, from the fuel consumers' point of view, the most important factor is the price at the pump — this will determine whether a renewable fuel will be widely used, but it is not the only consideration. One issue that was overlooked in this debate is that people prefer the path of least resistance, and thus will favour the easiest way to convert and store energy. Agriculture has been a part of human culture for millennia — we know how to grow plants. But biofuels have drawbacks: for example, they can be produced only in regions with plenty of arable land and ample food supplies. In addition, the yearly solar conversion efficiency of crop plants averages less than 1% (although this varies over the course of the growth cycle)[3]. The low rate of production of biofuels and their geographic dependence are not sustainable, especially given our planet's growing population.

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Commercial photovoltaic cells convert energy more effectively than biofuel crops, and Michel proposed them as a solution to our energy needs[4]. However, this technology is not suitable for all applications, or appropriate for all parts of the world. A major problem is the lack of a good way to store the energy with a density approaching that of gasoline. In the long term, we need to invest in artificial photosynthesis — the conversion of sunlight to chemical energy, stored in molecular bonds within a fuel. Artificial photosynthesis requires less land than biofuel crops and has a higher production rate, so it will probably be our primary source of renewable fuel in the future.

Hen Dotan: Throughout the debate, Chu emphasized the cost of alternative fuels. But how do you know the cost of an emerging new technology? For example, when silicon photovoltaic cells were first produced in 1954 they were very expensive (US$1,785 per watt) and inefficient (about 6% in the lab, but 2% for commercial products). But, with government subsidies and time, the price of these cells dropped to just $0.78 per watt in 2012, with their efficiency surpassing 25%.

Michel argued that biofuel research should be abandoned because photosynthesis is inefficient and energy crops compete with food crops for limited resources such as fresh water, arable land and fertilizer. I agree and I think that artificial photosynthesis is a better way forward; as in natural photosynthesis, the first step is to split water into oxygen and hydrogen using solar radiation. The hydrogen can be used directly as fuel or combined with carbon dioxide to produce methanol or other hydrocarbon fuels. This process has a theoretical efficiency of more than 15% — significantly higher than natural photosynthesis. In the last year, solar-to-hydrogen conversion efficiency has reached almost 5% using a cheap iron-oxide-based photo-anode[5]. Artificial photosynthesis devices are already mature enough to be implemented in remote locations where it is difficult to supply conventional fuels. Further progress, stimulated by government subsidies, could make this technology competitive with fossil fuels within ten years.

Mayes: We would all love to have a renewable energy technology that is inexpensive, works everywhere and has no drawbacks. Unfortunately, contrary to what Dotan is saying, none exists; if it did, fossil fuels would be a distant memory. There are drawbacks to each renewable energy technology. Fortunately, we do not need one technology to solve all our energy needs; we can use many, choosing the most appropriate for each situation.

I disagree that we should abandon research into biofuels. Next-generation biofuels that use biomass or waste, and don't interfere with our food supply, are almost here. Additional investment in biofuel technology will help to drive costs lower. To continue tackling the difficult problem of climate change, we should invest both in a wide range of near-term, near-market technologies, such as biofuels, and in basic science research, which will lead to unforeseen technologies.

Sheehan: Dotan is being optimistic: science may be able to find a solution, but if the basic idea is not cost effective a technology will never be widespread regardless of how much production is optimized. New technology has to take into account the abundance of the resources it uses. For example, silicon solar cells use the second most abundant element in the Earth's crust. It's doubtful that solar cells would be as widespread as they are today if they relied on rarer elements such as gallium or indium.

"New technology has to take into account the abundance of the resources it uses."

Now look at the technology for splitting water into oxygen and hydrogen. An ideal water-splitting cell is made using rare earth elements, which are expensive and scarce. Fifteen years ago, such systems achieved efficiencies of 12.4% (ref. 6), but research switched to technology that uses more abundant compounds such as iron oxide[7]. Even using abundant elements, however, the estimated cost of hydrogen produced by the 'artificial leaf' is around US$6.50/kg; hydrogen produced by steam reforming of hydrocarbons costs less than $2.00/kg (ref. 8). While I agree that artificial photosynthesis will be our long-term energy provider, this technology is not ready. Plenty of basic research needs to be done first. Until then, biofuels remain a viable fuel option.

Dotan: While I agree with Sheehan that price is an important factor for consumers, I would add that many people are bad at understanding long-term costs. For example, consumers still buy cheaper incandescent light bulbs, even though switching to energy efficient light bulbs can lower their total domestic electricity consumption by as much as 10%. Such is this disparity in short-term versus long-term cost that governments around the world are starting to ban incandescent light bulbs. This is an example of a free market failure, and I fear that biofuels could well become a second example — that is, that their short-term appeal will outweigh their long-term problems in the eyes of consumers.

Biofuels possess two major drawbacks. First, as noted, their production is inefficient. Second, biofuels still lead to polluting vehicle exhaust emissions. Depending on fuel type, these emissions might be lower than for conventional fossil fuels (although the evidence is currently inconclusive) but they are not pollution-free. I believe that artificial photosynthesis is already more efficient than biofuels and this process produces hydrogen, which is truly a zero-emission fuel (the only byproduct of burning hydrogen is water). Unfortunately, without proper regulation of biofuels and proper support for artificial photosynthesis, I worry that fossil fuels will be replaced by inefficient and polluting biofuels despite there being a better alternative. Even if global regulations limit biofuel feedstock to agricultural and forest wastes, as suggested by Mayes, we must focus on artificial photosynthesis research and implementation to ensure sustainable fuel production. ■

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LAUREATES

Steven Chu was co-awarded the Nobel Prize in Physics in 1997 for his work developing methods to cool and trap atoms using lasers. He served as the US Department of Energy secretary from 2009 to 2013, and has since returned to Stanford University in California.

Hartmut Michel was co-awarded the Nobel Prize in Chemistry in 1988 for elucidating the action of membrane-bound protein in photosynthesis. He is based at the Max Planck Institute of Biophysics in Frankfurt, Germany.

RESEARCHERS

Hen Dotan is a PhD candidate at the Department of Materials Science and Engineering of the Technion – Israel Institute of Technology in Haifa. His research is on solar hydrogen production by photoelectrochemical water splitting.

Heather B. Mayes is a PhD candidate in the Department of Chemical and Biological Engineering at Northwestern University in Evanston, Illinois. She is studying the molecular reactions that can convert non-food biomass into renewable energy and chemicals.

Stafford W. Sheehan is a graduate research fellow in the physical chemistry PhD programme at Yale University in New Haven, Connecticut. His research explores materials science, catalysis and artificial photosynthesis.

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